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Hyperthyroidism

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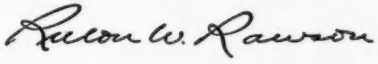

developed an interest in endocrine physiology as an undergraduate student, and took active part in studies on thyroid physiology under Dr. Paul Starr while a student at Northwestern University Medical School. Following his hospital training, he continued his studies in the laboratories of Dr. Joseph C. Aub at the Huntington Memorial Hospital and then of Dr. J. H. Means at the Massachusetts General Hospital. At the Massachusetts General Hospital he was in charge of the Thyroid Clinic and laboratory for seven years. Since 1948 he has been a member and Chief of the Division of Clinical Investigation in the Sloan-Kettering Institute. He has also been an Attending Physician and Executive officer of the Department of Medicine of Memorial Center. His academic rank at present is that of Professor of Medicine, Sloan-Kettering Division of Cornell University Medical College. His major investigative interests are in the field of thyroid physiology and the endocrine aspects of neoplastic disease.

HYPERTHYROIDISM and thyrotoxicosis are synonymous labels attached to a group of clinical pictures which can often be distinguished on the basis of clinical or anatomical features.

The most common of these maladies is variously known as exophthalmic goiter, Graves' disease or Basedow's disease. Since many patients with this disease have hyperfunctioning goiters without exophthalmos and some have exophthalmos without goiters, we prefer to use an eponym in labeling this syndrome. We prefer the eponym Graves' disease probably because of its common usage by the English-speaking medical profession and because Graves was the first to publish in detail his own observation of the disease (1).

Another common syndrome which is associated with hyperthyroidism is seen in older people and is characterized by nodular goiter without exophthalmos.

There are two other groups of patients who present a clinical picture of hyperthyroidism but do not have enlargement of the thyroid gland. In one group the hyperthyroidism arises from a struma ovarii. The other group obtains increased levels of thyroid hormone by surreptitiously taking thyroid pills.

In this presentation, the four different syndromes of hyperthyroidism will be discussed separately.

GRAVES' DISEASE OR EXOPHTHALMIC GOITER

Etiology

The etiology of Graves' disease is not known. Furthermore, since the disease is not reportable, it is impossible to give its incidence or its geographic distribution. Since it appears to be as common today as it was before the widespread prophylactic use of iodized salt in the endemic goiter area and since its frequency on the sea coast appears to be as great as it is in the endemic goiter areas, one can say that its geographic distribution is not the same as that of endemic goiter.

Although we may encounter this syndrome at any age, it does occur most commonly between the third and fifth decades. It appears about four to five times as frequently among females as among males. It is not uncommon to encounter this malady in more than one member of a family. Boas and Ober (2) reported their studies of one family in which the disease occurred 11 times in three generations.

Hertz and Means (3) reported a series of patients who developed the classic picture of Graves' disease after having been on a weight-reducing regimen with or without administered thyroid. We have failed to elicit any specific dietary deficiencies in a similar group of patients.

The reports by Iversen (4) and Meulengracht (5) of a significant increase in this disease in Denmark after the German occupation during World War II suggests various clues as to possible etiologic factors. In conversations with these authors and other physicians from Denmark, we have been assured that there was neither starvation nor evidence of any dietary deficiencies in Den-

mark during the occupation. The only foods which they did not have were the citrus fruits.

One might also ask whether or not this apparent epidemic of Graves' disease can be related to the psychic traumas which would naturally come with the defeat and occupation of one's country. As one sees many patients with this malady, one is impressed by the frequency with which some psychic trauma apparently preceded the development of the syndrome. Other patients may give a history of some infection or of a physical trauma experienced shortly before the development of the disease picture. Because of inability to define such episodes more clearly or to repeat them experimentally in human subjects, it is impossible to state whether these stress situations are of etiologic importance or whether they are merely accentuated in a patient who is already thyrotoxic. Though we harbor certain doubts and reservations concerning the etiologic relationships of such alarms, we do sponsor a working hypothesis which, if correct, would be compatible with the stress theory. With this hypothesis we suggest that stresses act as trigger phenomena which cause release of thyroid-stimulating hormone (TSH) through some hypothalamic-pituitary pathway and subsequent stimulation of the thyroid which in those who develop the disease is more sensitive to TSH.

This theory has developed as the result of many laboratory studies in which it has been demonstrated that the administration of extracts of the anterior pituitary may result in the anatomical and physiological changes characteristic of Graves' disease.

The most serious argument against this thesis is the fact that thyrotrophic hormone cannot be demonstrated in the blood or urine of patients with untreated Graves' disease, whereas it can be demonstrated in greater than normal amounts in the body fluids of totally thyroidectomized patients (6). This discrepancy might be explained by the observation that slices of rabbit thyroid tissue, when bathed in physiologic media containing pituitary extracts, inactivates the thyrotrophic hormone but does not alter the gonadotrophic hormone. Similar explants of thymus or of lymph nodes, both of which tissues are characteristically enlarged in Graves' disease, are capable of inactivating about one-half as much TSH as are explants of thyroid. In these studies no other

control tissues have such an effect on thyrotrophic hormone (7).

In another similar investigation we have studied the effects of normal and pathologic human thyroid tissue on exposed thyrotrophic hormone (7). In this study we demonstrated that well involuted thyroids of patients with Graves' disease, removed after a maximum therapeutic effect had been obtained from iodide administration, inactivated twice the amount of TSH as did normal human thyroid tissue. The latter observation might suggest that the thyroids of patients with this malady are more sensitive to TSH than are the thyroids of normal human beings.

Notwithstanding the above observation, which may or may not support our present working hypothesis that the thyrotrophic hormone contributes to the genesis of this malady, proof is lacking and we still have to state that the etiology is unknown. However, a clarification of the apparent increased reactivity of the thyroid in Graves' disease with the thyrotrophic hormone may throw some light on the etiology of this malady.

Pathology (Anatomical and Functional)

The most striking anatomical and functional changes occur in the thyroid gland. In patients with classic Graves' disease the thyroid is enlarged from two to several times the normal size. Though the enlargement is usually more or less symmetrical, the right lobe is often somewhat larger than the left. Such hyperplastic thyroids are very vascular and friable. On microscopic examination of such a diseased thyroid, the acinar cells are hypertrophied and hyperplastic, with marked increases in cell height. In most instances there is also a marked intrafollicular papillary infolding of the acinar epithelium. There is a loss of intrafollicular colloid which varies from a peripheral scalloping to complete elimination (Fig. 1, *A*, p. 21). Often in such thyroids one finds significant lymphocytic infiltration. This may vary from a sparse to dense infiltration by lymphocytes to the development of lymph follicles with germinal centers within the parenchyma of the thyroid.

The thyroids examined only after adequate treatment with iodides present quite a different anatomical picture. In the gross

they are usually firm and much less vascular. On microscopic examination they are involuted. The acinar cells are nearly normal in size and the papillary projections are almost absent. In some instances the effects of adequate treatment with iodides are so great as to result in hyperinvolution, with a microscopic picture suggestive of colloid goiter.

Untreated hyperplastic thyroids of this malady carry on the functions of the normal thyroid at an accelerated rate. They have an avid trap for iodide which is expanded over the normal. Presumably they oxidize iodide to iodine and bind it to the amino acids and proteins of the thyroid at an accelerated rate. Such hyperplastic thyroids release the thyroid hormone into the circulation very promptly without any significant period of storage in the follicles.

During recent years it has been amply demonstrated that the circulating thyroid hormone in experimental animals and in normal human beings is thyroxine. Rosenberg (8) was the first to demonstrate that thyroxine is the circulating hormone in patients with Graves' disease. Recently Gross and Pitt-Rivers (9) demonstrated triiodothyronine in the sera of animals and humans at varying intervals after they had received radioactive iodine. They have suggested that triiodothyronine is a peripheral metabolite of thyroxine which exerts the primary hormonal action. This compound has also been demonstrated in the sera of patients with Graves' disease. In thyrotoxic patients the total circulating thyroid hormones may be slightly increased to four or five times the normal level. Such increased blood levels of thyroid hormone produce the characteristic increased rate of metabolism of hyperthyroidism.

Although the most dramatic anatomical and physiological changes of this malady are found in the thyroid, the structural and functional changes are by no means limited to this organ.

One of the most challenging features of the disease is found in the eyes, which are sometimes dangerously proptosed. Except for corneal ulcerations which may occur in those patients who are unable to close their eyes, there are no pathologic changes in the eyeball. The major changes which occur within the orbit but behind the eyeball are not well defined. Indeed, opportunities

for studying these areas developed only after Naffziger (10) described a surgical decompression of the orbit as a treatment for "malignant" exophthalmos. Naffziger and his associates (11) reported that the orbital muscles in these patients are swollen and edematous, being three to eight times the size of normal extraocular muscles and thus increasing the intraorbital tension. Biopsy of such muscles showed edema, round cell infiltration, increased fibrous tissue, hyalinization and fragmentation. Rundle and Pochin (12) studied the eyes and orbital contents of 17 patients who had died of Graves' disease. They reported that such eyes contained more fat than is found in the normal orbit and suggested that exophthalmos is due to an increased deposition of fat. The discrepancies between the observations of these two groups of workers probably stem from the fact that the two studies were done in the same disease but in different stages and with different techniques. It seems quite possible that the severe exophthalmos of this malady is due to orbital fat, edema and increased muscle mass. The diseased orbital muscles probably possess less tensile strength and are thus less capable of resisting the increased intraorbital pressure. The characteristic stare and lid lag of this malady which usually disappear following correction of the hyperthyroidism cannot be related to the retro-orbital changes described above. The evidence suggests that they must be attributed to a spasm of the palpebral muscles. Pochin (13) attributes these changes to a spasm of the levator pelpebrae superioris, a striated muscle innervated by the oculomotor nerve. Mulvaney (14) attributes the stare and lid lag to a spasm of Landstrom's muscle, a smooth muscle innervated by sympathetic nerve fibers.

Notwithstanding the frequently observed decrease in lid lag and stare following correction of the hyperthyroidism in patients with Graves' disease, the proptosis does not regress. Indeed, by measurement the proptosis actually increases in most of such patients following thyroidectomy. On the basis of studies on animals it has been postulated that the exophthalmos is due to an action of thyrotrophic hormone. In studies by several investigators (15, 16), exophthalmos has been produced in various species by administering pituitary extracts rich in thyrotrophic

hormone. Since most of these pituitary extracts were crude and impure, we cannot ascribe the exophthalmic effects to the thyroid-stimulating hormone per se. Recently, Dobyns and Steelman (17) were able to produce exophthalmos in the fundulus with a pituitary extract which possessed no thyroid-stimulating properties.

The anatomical changes found in the extraocular muscles have also been described in other skeletal muscles. It was in 1898 that Askanazy (18), a German pathologist, first described fatty infiltration, loss of striations and degeneration of the muscle fibers in patients suffering with this malady. Dudgeon and Urquart (19) described an infiltration of plasma and endothelial cells in the atrophied skeletal muscles of such patients. Such anatomical changes no doubt explain in part at least the muscle weakness which is so common in Graves' disease. It is possible that the creatinuria and poor tolerance for administered creatine so characteristic of this malady are likewise related to such structural changes in the muscles. It is of interest that myasthenia gravis, which is characterized by similar microscopic changes in the muscles, is not infrequently associated with Graves' disease.

The administration of thyroid in toxic amounts to rats may cause a loss of skeletal muscle mass but does not produce the microscopic changes described above. Such changes have been produced, however, in the muscles of intact and of thyroidectomized guinea pigs upon the administration of pituitary extracts rich in thyrotrophic hormone (20, 21). Thus we might explain the fact that the muscle symptoms oftentimes cannot be correlated with the severity of the hyperthyroidism.

There does not appear to be any uniform picture in the heart muscle. Hypertrophy of the heart muscles is often found in patients dying of this disease. Although some authors have reported fibrotic and lymphocytic changes in the myocardium in fatal cases, others have failed to find any characteristic anatomical changes in the heart.

The cardiac rate and output are increased in spontaneous or induced hyperthyroidism, whereas they are decreased in myxedema. In long standing hyperthyroidism or in patients whose hyperthyroidism is complicated by pre-existing organic heart

disease, fibrillation and frank heart failure frequently ensue.

The mechanisms by which the cardiac changes are produced are not clear. The most common explanation is that the increased rate of metabolism increases the circulatory demands and results in an increased work of the heart to meet the organism's needs. Rasmussen (22), however, studied the hearts of dogs made thyrotoxic by the administration of thyroxine or of desiccated thyroid and reported that he was unable to correlate the changes in metabolic rate with the changes that he observed in the hearts of his animals. Furthermore, animals whose metabolic rates he increased with dinitrophenol did not manifest significant changes in heart function. He suggested that there is a specific cardiotoxic effect of the thyroid hormone. The Hoffmans (23) reported that the hearts of several experimental animals made thyrotoxic by the administration of thyroid hormone were insensitive to vagal stimulation. This mechanism may account for the relative insensitivity that thyrotoxic patients with cardiac failure have for digitalis. Another possible mechanism which would contribute to the high cardiac output in patients with large goiters might be attributed to an arteriovenous shunt through a very vascular thyroid.

Beaver and Pemberton (24) reported that the livers of 107 patients who died of Graves' disease had a high incidence of fatty infiltration and focal necrosis. Atrophic changes were also noticed in the livers of nearly half of these patients. Experimentally, some of these changes can be produced by administering large doses of thyroid over a long period. The administration of pituitary extracts rich in thyrotrophic hormone to thyroidectomized guinea pigs has been noted to produce fatty liver followed by some round cell infiltration and fibrosis (21). One must also consider the possibility of these changes occurring as the result of a nutritional deficiency.

Enlargement of the thymus and lymph nodes has been described as characteristic anatomical changes in patients who have died of this malady. Warthin (25) was so impressed by the thymico-lymphadenopathy of Graves' disease that he labeled it the Graves constitution. Having observed that explants of thyroid, thymus and lymph nodes are the only tissues which inactivate

the thyrotrophic hormone, we have suggested that the thymus and lymph nodes are target organs of TSH.

Of course one must also consider the possibility that the thymico-lymphadenopathy is due to some insufficiency of the adrenal. LeCompte (26) has reported that the width of adrenal cortices in patients who had died of Graves' disease was less than that of adrenals taken from people who had had no thyroid disease. It has also been reported (27) that patients with Graves' disease when given ACTH manifest minimal responses as evidenced by changes in the circulating eosinophils.

Symptomatology

The presenting symptoms may vary from none to those of fulminating thyrotoxicosis with many systems of the body affected. Those patients who admit to no symptoms may even insist that they feel better than they have at any time previously. Such patients are usually males who actually feel exhilarated by the increased levels of thyroid hormone and who usually consult the physician primarily to satisfy a friend or relative who has noted prominence of the eyes, a goiter or increased excitability of the patient. Other patients whose disease is manifest primarily by the ophthalmic symptoms may first consult an ophthalmologist because of symptoms referable to the eyes. Some older patients may present themselves primarily because of symptoms of cardiac failure. We have seen one male patient who presented himself to the clinic with gynecomastia fearing that he had a cancer of the breast.

Although it is not common, we do see patients with fulminating Graves' disease in whom all of the symptoms and findings of the disease have developed within a few days. Recently we had an opportunity to study a 40-year-old woman who developed a full-blown picture of moderately severe Graves' disease while in the hospital recovering from a panhysterectomy.

On the other hand, we may see patients who have had the disease with exacerbations and remissions for many years, who finally present themselves because of some complication such as heart failure or even impending thyrotoxic crisis.

The most commonly seen picture, however, is that of a woman who presents a fairly classic picture of the disease which has been developing over a period of eight to nine months.

The symptoms described in the presenting complaint or those elicited in a careful review of systems illustrate the many and varied actions of the thyroid hormone with changes in practically every system of the body.

Notwithstanding the fact that many patients experience some exhilaration in the early stages of the disease, most of them, by the time they consult a physician, complain of nervousness and increased excitability. They may cry more easily than previously or have poor control of their tempers. Frequently, they complain of tremors on lifting a cup of coffee or other small objects. On examination such patients usually have a tremor of the outstretched hand. This tremor is a fine and rapid one. Some of the older patients may exhibit a coarse but rapid tremor. The excitability of these patients, when considered with the stare and lid retraction, impresses one with a picture of fear or even anger.

Some of the most common symptoms of this malady are those related to the cardiovascular system. They may vary from a palpitation which is most noticeable with excitement to the symptoms of frank cardiac failure. Although the blood pressure is not characteristically elevated, the pulse pressure is usually increased. This elevation in pulse pressure as a rule can be related to a slight increase in systolic pressure and a slight decrease in diastolic pressure. The heart size is not characteristically increased. The heart sounds may be perfectly normal except for the rapid rate, which usually is 90 or more a minute. In males it is not as rapid as in females. We often find an apical systolic murmur of mild to moderate intensity. Rarely we find a diastolic murmur at the apex which disappears on correction of the hyperthyroidism. One very characteristic sign of hyperthyroidism is a systolic scratch heard over the second to third interspace just to the left of the sternum. This scratch is usually heard at the end of inspiration, though it may also be heard at the end of expiration. Bounding carotids may be seen and the pulse is usually quite full and rapid.

Some patients present themselves primarily because of a goiter.

Women complain of it because of its undesirable cosmetic effects. Men, if they complain of it, usually say that it has increased in size enough to make their collars intolerably tight. On physical examination the thyroid of a patient with Graves' disease is invariably enlarged to some extent. This enlargement may vary from two times to many times its normal size. On careful examination the gland is more or less symmetrical, though the right lobe is often larger than the left. The trachea as a rule is not displaced to one side or the other. The gland is meaty in consistency. The pyramidal lobe, which as a rule is found on the left side of the trachea, is enlarged. Characteristically, the gland is vascular, and we are able to demonstrate a bruit over the upper or lower poles of either lobe. In the more vascular glands we may feel a thrill over either the upper or lower poles. The gland of a patient who recently has been treated with iodides will feel firm and rubbery in consistency.

The patient with classic Graves' disease will usually complain of some intolerance for heat. If he does not, he frequently will state that he has a greater tolerance for cold than previously. Such symptoms may be so subtle that the patient simply reports that he needs fewer bed clothes than he previously required or that in rooms where other occupants are quite comfortable, he wishes to have the windows and doors opened. Such patients likewise complain of increased sweating.

On examination the skin is often warmer than normal; indeed, if one finds a cool skin in a patient suspected of this malady, the diagnosis becomes doubtful. The skin is oftentimes wet and moist. Characteristically, the skin has a velvety texture. Occasionally, women who have or have had the disease complain of a thinning of the hair. Vitiligo is frequently found on the skin. Naturally, this change is more prominent on the hands or other exposed surfaces. It is of interest that these patients usually state that they have had the vitiligo for many years before the onset of the present malady. The author has often been impressed by loss of hair over the lower third of the legs of these patients.

A loss of weight, notwithstanding a normal or increased caloric intake, is almost a cardinal symptom of hyperthyroidism. Rarely, we see patients whose dietary intakes are so great as to protect

them against any loss of weight. The weight loss is readily explained on the basis of the increased metabolic rate. Frank diarrhea is not common. However, most patients with Graves' disease admit to a change in bowel habits; that is, they may have two stools instead of one per day and stools which are softer than normal. It is of interest that peptic ulcers are most uncommon in patients with hyperthyroidism. There are no characteristic findings in the gastrointestinal tract. However, on examination of an extremely ill patient with hyperthyroidism of very long standing, one may find evidence of liver damage.

Weakness is also characteristic and in some patients may be the primary complaint. The weakness can be demonstrated by having the patient in the sitting position hold his leg in the extended position. As a rule a patient with Graves' disease is unable to hold his leg in this position for longer than one minute and a half. Rarely we see patients whose weakness is so profound that they have difficulty in lifting themselves off of the bed. Such weakness is an ominous sign and demands prompt and effective treatment.

Wasting of various muscle groups is a characteristic finding in this disease. It is often most striking in the temporal muscles or in the muscles of the shoulder girdle or of the legs.

The patient who makes careful observations will often tell of some polyuria and increased thirst which disappears on control of the hyperthyroidism. There are no other urinary symptoms or urinary findings which can be related to this malady.

Oligomenorrhea is the usual complaint in premenopausal women with this disease. Rarely, amenorrhea is a major complaint which is corrected after the hyperthyroidism has been adequately controlled. There is no evidence that the fertility of such patients is significantly altered.

Male patients with this malady seldom note a change in gonadal function. We have seen a few patients, however, who did complain of impotence. On the other hand, it has been reported in the lay press that a recently discovered portrait of Casanova, the great lover, demonstrated some exophthalmos and other signs suggesting that this accomplished gentleman had Graves' disease. Gynecomastia is quite common in males suffering

with this malady. Indeed, we have the impression that if one looks for it very carefully, one will find it more frequently than not in those males who have exophthalmos as a major component of their Graves' disease. Such gynecomastia is usually characterized by a thickening of the subareolar tissue which on palpation oftentimes is tender. We have seen the gynecomastia so exaggerated that the patients' breasts were not unlike those of a pubescent girl. It is of interest that we have observed four female patients in the last few years who reported that with the onset of moderately severe exophthalmos, their breasts had so increased in size that they had to wear larger brassieres.

The ophthalmic symptoms in the majority of these patients are not distressing. Often the average patient will state that a member of the family or friend has noted a prominence of his eyes. The only complaints may be of increased tearing on awakening or on exposure to cold or wind.

Examination of the eyes reveals dilated pupils with a widening of the palpebral fissures and rather infrequent or irregular blinking. The widened palpebral fissures give the appearance of a stare which has been likened to the facies of fright or even rage. Although there frequently is a true exophthalmos, one may be deceived by the lid retraction and interpret it as a proptosis. This stare, which is usually benefited by controlling the hyperthyroidism, has given the impression that thyroidectomy corrects the exophthalmos of hyperthyroidism. There is usually a lag of the upper lid on looking downward and a lag of the globe behind the lids on looking upward.

Complications

Ophthalmopathic Graves' disease and hyperophthalmopathic Graves' disease are terms which have been given to certain complications that fortunately occur not too frequently. Although the patient with a classic case of Graves' disease presents both a goiter with hyperthyroidism and exophthalmos, some patients present only the picture of hyperthyroidism without eye signs. On the other end of the spectrum we find an unfortunate group of patients who present only the very troublesome ophthal-

mopathy of this malady. We have seen patients who during the period of follow-up have developed at different times all of the above phases of the disease.

Certainly the ophthalmopathic phase, when it occurs, is a very troublesome one which, if not handled properly, may result in serious complications. It may also be a major complication of an otherwise uncomplicated course of hyperthyroidism subjected to treatment with surgery or other thyroid-inhibiting or ablative procedures.

This complication is relatively more common in males than in females. To be more explicit, Graves' disease is more common among women, but males with this malady are more likely to develop the ophthalmopathic features of the disease than are women.

Notwithstanding the fact that most patients who have this distressing complication of Graves' disease develop ophthalmopathy following ablation of their thyroids, we do see a number of patients whose ophthalmic symptoms are primary. These people usually seek help first from the ophthalmologist. The first symptom may be of unilateral proptosis. More commonly, however, these patients complain of excessive tearing and blurring of vision. Frank diplopia which is exaggerated or experienced only on looking upward or to one side or the other is a common complaint. A sensation of a foreign body under the lids is often described. A sense of pressure behind the eyes is an infrequent symptom. Commonly, these patients will state that all of their subjective symptoms are worse on arising and that they are less severe toward mid-day.

Although we have seen this primary feature of Graves' disease in patients with large goiters and severe hyperthyroidism, it occurs more commonly in patients with very mild hyperthyroidism. We do see it also in patients who are euthyroid or even hypothyroid.

On examination the eyes of these patients are usually moderately to markedly proptosed, with exophthalmometric measurements of 23–32 mm., the normal being 14–17 mm. Edema of the lids is the rule. The upper lids frequently present a finger-like projection with the maximum swelling presenting on the nasal side of the eye. The conjunctivae are often reddened and edema-

tous. By having the patient look toward the opposite side, one can usually demonstrate a reddened and swollen external rectus muscle at the site of insertion. By having the patient move his eyes in all directions, one can frequently demonstrate limitation of movement in at least one direction. Limitation of upward and of outward gaze is not uncommon. Diplopia may not be demonstrated until the patient attempts these motions. If one presses lightly over the closed eye balls, one usually finds resistance to the pressure in contrast to the normal resiliency. Indeed, this test we believe is a valuable method of evaluating the progress of a patient with severe exophthalmos. Occasionally the proptosis in these patients is so great that they are unable to close their eyes. Corneal ulceration with its complications of infection may lead to the loss of an eye in such patients unless the eyes are adequately treated and protected.

Cardiac failure is one of the more common and serious complications of hyperthyroidism. Indeed, our colleagues, the cardiologists, list the thyrotoxic heart as one of the varieties of heart disease. Whether the heart in the so-called thyrocardiac patient fails because of exhaustion as the result of an extra work load or because of a cardiotoxic effect of the thyroid hormone is not clear. The reason for heart failure is most commonly explained on the basis of an increased total body metabolism which increases the demands of the heart and circulation. This increased blood flow is produced not only by an increased cardiac rate but also by an increase in volume output. In the patient with a hyperplastic and very vascular thyroid it is quite possible that at least some of the increase in heart rate and cardiac output is due to some arteriovenous shunt with blood rushing through the widely dilated vessels in the thyroid. At any rate a constant overactivity of the heart is necessary to maintain the constantly increased blood flow. Although cardiac enlargement does not occur regularly in patients with Graves' disease, the persistent overactivity of long-standing hyperthyroidism may lead to some increase in heart size. Eventually in patients with hyperthyroidism of long duration or with complicating valvular heart disease, hypertensive or arteriosclerotic heart disease, this persistent overactivity of the heart can cause fibrillation and frank heart failure.

In several series of thyrotoxic patients the incidence of paroxysmal or permanent auricular fibrillation has been noted in 3–10 per cent of cases. In similar series of cases the incidence of congestive failure has varied between 4 and 20 per cent. The incidence of fibrillation and of congestive failure increases with increasing age of the patient. Hurxthal (28) attributed congestive failure in hyperthyroidism to (*a*) age and coexisting cardiovascular changes, (*b*) the specific heart drive incited by the thyrotoxicosis, (*c*) auricular fibrillation and (*d*) the duration and intensity of the hyperthyroidism. It is of interest that Lahey and Hurxthal (29) in a study of the postoperative end results in 300 "thyrocardiac" patients observed that 71% of those who were fibrillating were restored to normal rhythm and 95% of those with congestive failure were restored to cardiac compensation by correcting the hyperthyroidism.

There are few distinguishing features of the congestive failure which are characteristic of the thyrotoxic heart. However, in addition to the usual symptomatology of hyperthyroidism which in the older age group may be more or less marked, though in failure, these patients usually manifest shortened circulation time. Another feature is that their cardiac failure is quite resistant to digitalis.

Thyroid storm or *crisis* is a rare but extremely interesting and serious complication of Graves' disease. It has been a very infrequent complication since the introduction of antithyroid agents such as propylthiouracil and methimazole. A large series of cases has been reported showing an incidence of 1.2 per cent in all the thyrotoxic patients admitted to the wards of the Massachusetts General Hospital (30). This covered the years subsequent to the use of iodine but prior to the use of antithyroid drugs. Although the cause of the thyroid storm is unknown, it has been regarded as "decompensated" thyrotoxicosis. This seems an apt analogy to the failure of the body to compensate for some injurious process, as in decompensated heart disease. Storms most commonly occur postoperatively (two thirds of McArthur's cases). The usual outstanding clinical feature is hyperpyrexia, which may reach 106–108 F. With this there are marked tachycardia, extreme agitation, profuse sweating and occasional vomit-

ing and diarrhea. Occasionally, the storm is manifested by less dramatic symptoms, and apathy, lethargy and prostration predominate. The gross mortality of patients in thyroid storm is approximately 65 per cent.

Psychoses of hyperthyroidism are infrequent but very troublesome complications. The psychoses of Graves' disease, like those of other endocrine abnormalities, do not follow any particular pattern. Indeed, some patients manifesting psychiatric complications of Graves' disease may fit into several patterns during a period of observation. The mechanisms by which they develop are unclear. At any rate it seems quite clear that the treatment of such psychoses should be directed at correction of the hyperthyroid state.

Diabetes mellitus, if complicated by Graves' disease, is unquestionably aggravated by the hyperthyroid state. Naturally, it is greatly improved by control of the hyperthyroidism. There are instances, however, in which frank diabetes develops after the onset of hyperthyroidism and is apparently corrected when the patient is brought to a state of euthyroidism. In such cases, after control of the hyperthyroidism and apparent cure of the diabetes mellitus, a glucose tolerance test will still reveal the latent diabetes.

Localized myxedema is a very strange lesion which complicates Graves' disease infrequently. We have never seen it except in patients who had moderately severe to very severe exophthalmos. Though it has been described as occurring on the forearms, we have seen it only on the legs, usually involving the lower third of the anterior aspect of the leg. It is associated with a loss of hair over that part of the leg. Oftentimes in patients with severe exophthalmos without localized myxedema, one observes a complete loss of hair over the lower third of the legs. Sometimes this epilation is localized to the outer aspect of the lower third of the leg. There may be a barely perceptible nonpitting swelling which has a purplish-red color over the area described. In the more severe cases there is a prominent area of nonpitting painless swelling which has a reddish to purplish color.

The mechanisms by which this complication occurs are far from being clarified. The term "localized myxedema" has been

given by virtue of the fact that mucin-like substances have been demonstrated in tissue samples taken from such lesions. Control of the hyperthyroidism does not improve the localized myxedema; indeed, such treatment may make it worse.

Diagnosis

No diagnosis is easier to make than that of Graves' disease in a tremulous, thin, nervous patient with exophthalmos and a goiter. On the other hand a tense anxious patient in whom many symptoms are suggestive and most tests are equivocal, the diagnosis is often most difficult. Graves' disease must be suspected in any patient with an enlarged thyroid. If the pyramidal lobe is enlarged and meaty, it is particularly suggestive. The symptomatology which is so varied may be most involved. One must suspect Graves' disease in the presence of any of the following symptoms: intolerance to heat or increased sweating; recent weight loss in spite of adequate to increased caloric intake; nervousness or hyperactivity; muscular weakness; tremor of the hands; cardiac failure, especially if it does not respond to digitalization.

Psychoneurosis is probably the most common clinical problem which has to be differentiated from Graves' disease. As a rule the multitude of complaints the patient with psychoneurosis presents should make one suspicious of the diagnosis of Graves' disease. Though some of these patients may complain of an increased appetite, they do not have weight loss. If they do have weight loss, there is usually no increase in appetite as we find in patients with Graves' disease. The basal metabolic rate, which may be elevated, is not associated with an increase in blood iodine nor with some of the other more classic laboratory findings which will be discussed later.

Neurocirculatory asthenia with its classic symptoms of palpitation, precordial pain, dyspnea, faintness, dizziness, tremor, sweating and nervousness poses a problem for differentiation from Graves' disease. Though patients with this malady are frequently referred with the diagnosis of hyperthyroidism, thyroid disorder is usually ruled out by a normal weight and dietary intake, a cool skin and by the absence of goiter. A normal blood iodine level

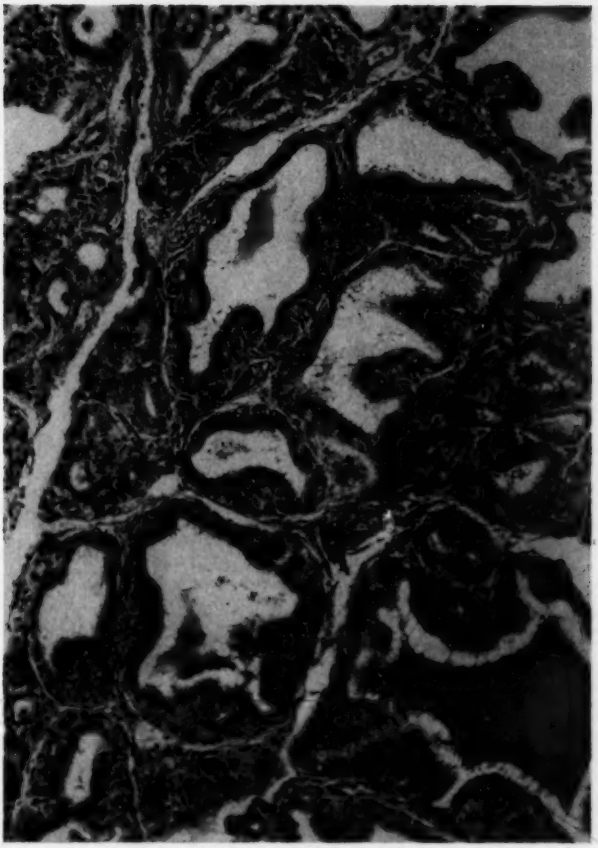

FIG. 1, *A*.—Effect of iodine of thyroid of patient with Graves' disease under influence of thiouracil. Biopsy of thyroid before beginning treatment. BMR + 44%; mean acinar cell height 15.3 microns.

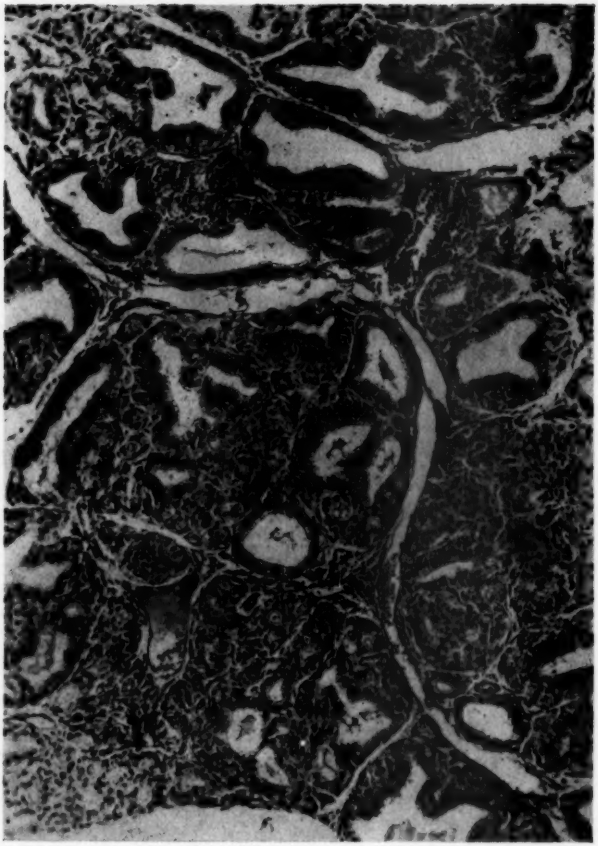

FIG. 1, *B.*—Biopsy of thyroid after treatment with thiouracil; 600 mg. daily had resulted in BMR of + 8%; mean acinar cell height 17.3 microns.

FIG. 1, *C*.—Representative section of thyroid removed after continued treatment with thiouracil, 600 mg. daily, and sodium iodide, 300 mg. daily. Mean acinar cell height 10.3 microns.

and avidity of the thyroid for radioiodine usually satisfy the patient and referring doctor that the patient does not have Graves' disease.

Hypertensive cardiovascular disease may occasionally represent a difficult problem to be differentiated from Graves' disease. In the latter condition moderate elevation of the systolic blood pressure is common and coexistence of the two diseases is not uncommon. Hypertension alone may elevate the basal metabolic rate. The most helpful tests in differentiating these two maladies are the serum protein-bound iodine and a tracer study with radioiodine.

Pheochromocytomas may simulate Graves' disease because of the signs associated with an increased level of circulating adrenaline, i.e., nervousness, palpitation and loss of weight. Differentiation is made even more difficult by the fact that these patients usually have elevated basal metabolic rates. A normal serum protein-bound iodine level with a normal uptake of radioiodine will rule out hyperthyroidism in such patients. The demonstration of an increase in blood pressure following the administration of histamine or of a fall in blood pressure following the administration of agents such as benzodioxane or Regitine gives strong support to the diagnosis of pheochromocytoma. Recently it has been demonstrated that patients with pheochromocytomas characteristically excrete markedly increased amounts of catecholamines in the urine (31).

Chronic alcoholism may result in symptoms which suggest Graves' disease. The weight loss, perspiration and tremor of the hands of these patients are often associated with an increased basal metabolic rate. Oftentimes if a patient has an endemic goiter, hyperthyroidism can be ruled out only by a normal blood iodine value or a normal uptake of radioactive iodine.

We have, however, seen alcoholics who had *portal cirrhosis* associated with weight loss, nervousness and elevated basal metabolic rate who also concentrated greater than normal amounts of radioiodine in their thyroids. Mueller and associates (32) have reported that a high percentage of patients with portal cirrhosis have a high uptake of radioactive iodine. The mechanisms of this phenomenon have not been clarified.

Myasthenia gravis is occasionally confused with Graves' disease. Diplopia and muscle weakness are common in both diseases. Furthermore, myasthenia gravis occurs occasionally in patients who have Graves' disease. The dramatic improvement in patients with myasthenia gravis given prostigmine is diagnostic and does not occur in patients with classic uncomplicated Graves' disease. The enlargement of the thyroid associated with an elevated basal metabolic rate and serum protein-bound iodine and an increased uptake of radioiodine by the thyroid usually will establish the diagnosis of Graves' disease in such patients.

Diarrhea due to chronic ulcerative colitis, sprue or certain neoplasms of the large bowel may be confused with Graves' disease. Usually careful study of the stools and bowel will reveal the cause of the diarrhea and careful study of thyroid function will usually rule out Graves' disease.

The increased cardiac output due to multiple arteriovenous shunts in patients with widespread *Paget's disease* may suggest hyperthyroidism in those patients who also have endemic goiters. Normal blood iodine values with the elevated serum alkaline phosphatase levels and x-ray findings of Paget's disease usually differentiate these two maladies to the satisfaction of everyone concerned.

Laboratory Diagnosis

Although in many instances the diagnosis of Graves' disease can be made without any question purely on the basis of clinical history and physical findings, several laboratory procedures are diagnostic or are helpful in determining the severity of the disease.

The basal metabolic rate is a well tried laboratory test which reflects the organism's response to increased or decreased levels of circulating thyroid hormone. In the usual classic case of untreated Graves' disease, the basal metabolic rate is elevated to levels which vary between plus 30 and plus 60. Rarely we may see true basal rates above plus 80. It must be pointed out that a patient's first experience with this test is not a pleasant one and that the first metabolic rate obtained on a nervous but euthyroid patient is frequently elevated. Bartels (33) has advocated deter-

mining the metabolic rate on frightened patients after they have been put under sedation.

The blood cholesterol value is usually normal or slightly below normal in this disease. We have, however, seen patients whose symptoms were predominantly ophthalmic who had slightly to moderately elevated blood cholesterol levels.

The serum protein-bound iodine (PBI) is characteristically elevated in patients having hyperthyroidism. In most clinics, levels of 7.5 micrograms per 100 cc. or more are considered diagnostic of hyperthyroidism. It must be recognized, however, that the previous administration of iodides or iodine-containing compounds will give spuriously elevated levels. The ingestion of Lugol's solution, saturated solution of potassium iodide or iodide-containing cough syrup will cause an elevation of serum inorganic iodides which may persist as long as 10–14 days after the medication is stopped. Spuriously elevated levels of PBI may be found in patients who have had x-ray studies following the administration of certain iodinated dyes. The increased levels of PBI may be found for months after a patient has received Lipiodol or the usual dyes employed for visualization of the gallbladder. The dyes used to visualize the urinary tract cause an elevation in PBI which usually lasts less than 24 hours.

Tracer studies with radioactive iodine in untreated patients with Graves' disease reveal an increased concentration and retention of the isotope in the thyroid or a decreased urinary excretion of the tracer. Another method of evaluating thyroid function with radioiodine is that of following the rate of turnover of the iodine by determining the ratio of protein-bound radioiodine to inorganic radioiodine at varying intervals.

A decreased tolerance for creatine in patients with Graves' disease has been standardized and utilized as a diagnostic test in this disease. Whereas euthyroid human subjects excrete less than 30 per cent of a standard dose of creatine, patients with Graves' disease excrete 50 per cent or more of the same dose.

One nonspecific laboratory finding that we always look for in patients with Graves' disease is a relative to absolute lymphocytosis, which usually occurs with normal to slightly depressed total white blood counts.

Treatment

Following the demonstration by Plummer that the administration of iodides made surgical thyroidectomy a safe procedure, surgery became the standard form of therapy. Today, however, we have several forms of treatment to choose from, and the clinician should consider each case individually before deciding which form he should recommend.

We have a variety of goitrogenic thyroid inhibitors such as propylthiouracil, methylthiouracil, methyl mercaptoimidazole and potassium perchlorate which prevent the production of thyroid hormone.

The most popular of these agents are propylthiouracil and methyl mercaptoimidazole which act by preventing the oxidation of iodide (Fig. 2) and thus interfere with the synthesis of thyroid hormone as long as they are administered in adequate dosage. Although many patients have realized remissions in their disease after prolonged treatment with these agents, recurrences are too common to justify hopes for many permanent cures with this modality. The best results are obtained in the premenopausal female with classic Graves' disease whose thyroid is only moderately enlarged. The poorest results have been obtained in males and in patients with very large goiters.

The most important place of these agents is in the preoperative preparation of the thyrotoxic patient for thyroidectomy. The advantages over preoperative preparation with iodides are that with these agents, one can bring the patient to euthyroid levels and thus the risk of thyroidectomy is no greater than that experienced in removing a nontoxic goiter. It must be recognized, however, that if one is to realize the advantages of these drugs as preoperative agents, one should administer them until the euthyroid state is attained.

The daily dosage of propylthiouracil or of methylthiouracil is 300 mg. until after the operation, when the drug can be stopped. Methyl mercaptoimidazole should be administered in a daily dosage of 20–60 mg. To maintain constant blood levels of these agents, the daily dose should be administered in divided doses at eight hour intervals. If one chooses to administer these agents

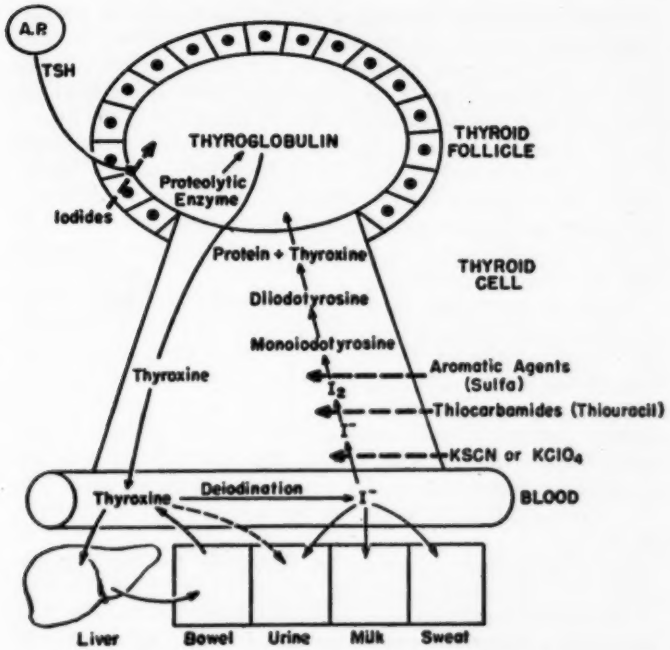

FIG. 2.—Pathways in metabolism of iodine and thyroid hormone and probable mechanisms of action on the thyroid of agents used in treating hyperthyroidism. Note that circulating iodide is trapped by the thyroid, oxidized to iodine and utilized in iodination of tyrosine and synthesis of thyroid hormone. The thyroid hormone is stored as thyroglobulin but is released into the circulation as thyroxine after proteolysis. Thiocyanate and perchlorate inhibit the iodide-trapping system of the thyroid cell. Thiouracil and related agents prevent oxidation of iodide to iodine. The sulfonamides and related aromatic agents prevent iodination of tyrosine. Iodides prevent the action of thyrotrophic hormone on the thyroid cell and presumably thus prevent the proteolysis of thyroglobulin.

over a long period in the hope of controlling the disease without surgery, the dose should be decreased to the minimal amount which exerts complete control after the euthyroid state is obtained. Since these agents act primarily to prevent the synthesis of thyroid hormone, one cannot expect a correction of the hyperthyroid state until after the thyroid hormone stored in the gland has been secreted and spent. Thus, if the patient has been previously treated with iodides, resulting in a storage of iodinated thyroglobulin, the time required for preoperative preparation will be much longer than in a previously untreated patient with a very hyperplastic thyroid.

Potassium perchlorate is another goitrogenic inhibitor of the thyroid which interferes with the synthesis of thyroid hormone. This agent inhibits the thyroid by suppressing the natural iodide trap of the thyroid (Fig. 2). A patient under the influence of this agent is unable to concentrate iodide in the thyroid and is thereby prevented from forming new thyroid hormone. This agent, like the thiouracil derivatives, has its greatest usage in the preoperative preparation of the thyrotoxic patient for thyroidectomy. This drug is prescribed in doses of 200 mg. every eight hours.

The disadvantage of preparing thyrotoxic patients for thyroidectomy with these goitrogenic agents are technical. They do not decrease the vascularity of hyperplastic thyroids. Indeed, they may even increase the vascularity and friability of the thyroid and thus make the surgeon's job not only difficult but even hazardous. The bleeding encountered in removing such vascular glands is in itself hazardous, but it may also so interfere with the surgeon's job as to increase the incidence of damage to parathyroids and recurrent nerves. Such disadvantages of this type of preparation can be overcome in most instances, however, by using iodides such as Lugol's solution or potassium iodide in addition to the goitrogenic drugs.

We prefer administering the goitrogenic agent alone until the patient has reached a euthyroid level. Then we add saturated solution of potassium iodide, 5 drops (300 mg.) daily, for another 10–14 days or until the gland becomes firm and the bruit disappears. With this regimen, the surgeon has a well involuted,

relatively avascular nontoxic thyroid which he can remove without the dangers encountered in operating on uncontrolled hyperthyroidism and with minimal risk of bleeding.

In view of the statement that thiouracil and its derivatives inhibit the utilization of iodine in the synthesis of thyroid hormone, the statement that iodides when administered with these agents will involute the thyroid requires some clarification. It can be explained by the fact that iodine exerts two actions on the thyroid. In the normal body economy iodide is ingested and circulates as such. It is concentrated by the thyroid's characteristically large trap for iodide, where it is oxidized presumably to iodine and then utilized in the synthesis of monoiodotyrosine, diiodotyrosine and thyroxine. The hormone is stored in the gland as a heavy iodinated protein, thyroglobulin. Upon demand of the organism for thyroid hormone, the thyroglobulin is hydrolyzed to thyroxine, presumably by a proteolytic enzyme. It is thought by many that this proteolytic enzyme is activated by thyrotrophic hormone (see Fig. 2). The role played by iodine in the synthesis of thyroid hormone, we might call its nutritive function. The requirement for this function is roughly 100 micrograms daily.

The pharmacologic effect of iodide in Graves' disease, we might call its involuting action. These two functions of iodine have been separated by demonstrating that the involuting effects of iodides occur in thyrotoxic patients receiving thiouracil in doses great enough to prevent the utilization of iodine in the synthesis of thyroid hormone (34). This was done in four patients who permitted us to biopsy their thyroids before instituting any treatment and again after optimal therapeutic responses had been obtained with thiouracil. The thiouracil was then continued, and sodium or potassium iodide in doses of 300 mg. daily was also administered until thyroidectomy was done 10 days later. The biopsies showed the classic hyperplasia of Graves' disease. By cell height measurement the second biopsy specimens showed even greater hyperplasia than did the first biopsy specimens. After treatment with thiouracil and added iodides, however, the glands showed classic involution with significant decreases in acinar cell heights (see Fig. 1, *C*). Chemical analysis of these glands demonstrated low levels of thyroglobulin iodine comparable to those

found in the thyroids of untreated patients with Graves' disease (Table 1). Thus involution of the hyperplastic thyroid is produced by iodides even though the iodine cannot be utilized in hormone synthesis.

We attribute this therapeutic effect of iodide in Graves' disease to an inhibition to the reaction between thyroid cell and the thyrotrophic hormone (see Fig. 2). This theory is supported by the fact that the inactivation of TSH by thyroid tissue is inhibited if iodide is added to the nutrient medium (7). It is further sup-

TABLE 1.—THYROID CELL HEIGHTS BEFORE TREATMENT, DURING THIOURACIL TREATMENT AND AFTER THIOURACIL PLUS IODIDE TREATMENT, AND THYROGLOBULIN IODINE VALUES OF THYROIDS REMOVED AFTER TREATMENT WITH THIOURACIL AND IODIDE

PATIENT	MEAN CELL HEIGHTS			THYROGLOBULIN IODINE, MG./100 GM. (WET WEIGHT)
	At Biopsy before Treatment	At Biopsy after Thiouracil	At Operation after Thiouracil + Iodide	
C. T.	12.6 ± 0.14	13.9 ± 0.14	6.2 ± 0.03	1.2
A. H.	11.1 ± 0.13	10.8 ± 0.13	7.4 ± 0.05	1.1
H. M.	13.9 ± 0.19	14.3 ± 0.15	8.2 ± 0.05	7.4
A. S.	15.3 ± 0.14	17.3 ± 0.17	10.3 ± 0.07	2.3

ported by the fact that whereas the untreated thyrotoxic patient excretes in the urine no active thyrotrophic substances, he does excrete significant amounts shortly after the institution of therapy with iodides.

In 1938, through the use of the newly discovered and perfected cyclotron, radioactive isotopes of iodine were prepared and their metabolism studied. The first isotopes used were I^{128} with a half-life of 25 minutes and I^{130} with a half-life of 12.6 hours. Later I^{131}, with a half-life of 8 days, was prepared in the cyclotron by the deuteron bombardment of tellurium. I^{131} is now obtainable as a fission product from the U.S. Atomic Energy Commission for study, diagnosis and treatment of thyroid disease.

Chapman and his associates (35) recently reviewed their 10 year experiences of treating hyperthyroidism with radioactive iodine. Of 400 patients treated with I^{131}, 8 per cent developed myxedema. Fifty patients required two or more therapeutic doses

of I^{131}, and 19 were better but still thyrotoxic six months after the first treatment. In patients who responded, the average interval between treatment and the development of a normal basal metabolic rate was two months. The average interval between treatment and the occurrence of myxedema was four months. However, some of the patients did not develop myxedema until several years after this form of treatment.

In our clinic it has been the practice to administer a dose of I^{131} which will deposit 150 microcuries of the isotope in each estimated gram of the thyroid. Thus, a typical patient with Graves' disease would be treated as follows:

$$\begin{aligned} \text{Tracer dose } I^{131} &= 70\% \text{ uptake in thyroid} \\ \text{Est. thyroid weight} &= 40 \text{ Gm.} \\ \text{Therapy dose} &= \frac{40 \times 150}{0.70} = 8{,}600 \ \mu\text{c or } 8.6 \text{ millicuries} \end{aligned}$$

In an analysis of 116 patients who had been treated according to this practice, we found that 23 per cent were hypothyroid and 16 per cent remained hyperthyroid after one such therapeutic dose of I^{131} (36). Further analysis of these patients, most of whom had had blood levels determined 48 hours after administration of tracer or therapeutic doses of radioiodine, demonstrated considerable variation in the rates at which the I^{131} left the thyroid presumably as thyroid hormone. Indeed, it was found that the half-life of I^{131} in the thyroids of these patients varied between 14 and 20 days. We are now taking this factor into consideration in planning the therapeutic doses of our patients. Following a tracer study which includes blood levels at 48 hours we are calculating the therapeutic dose from the following formula, which was derived from the data on 43 patients who became euthyroid after a single dose of I^{131}.

$$Y = 110 + 27\,B$$

where Y = microcuries to be deposited per gram of thyroid tissue at 48 hours, and B = concentration of I^{131} in whole blood 48 hours after the dose.

For calculation of a therapeutic dose from tracer data, the following is the complete equation.

$$D = \frac{100\,(110 + 27\,B) \times G}{U}$$

where D = dose to be given, in microcuries, G = weight of thyroid, in grams, and U = percentage uptake of tracer dose in 48 hours.

Notwithstanding the fact that radioactive iodine is very effective in controlling the hyperthyroidism of these patients, there are certain practical and theoretical considerations to be listed on the debit side.

The equipment is moderately expensive and should be used only by one trained in physics.

The full therapeutic effect after treating a hyperthyroid patient with radioactive iodine is frequently not realized for 10–12 weeks. This, however, is about the same period required to control the average patient with propylthiouracil.

Myxedema occurs in 4–20 per cent of the patients treated with radioactive iodine. This is not regarded as a serious problem, however, since replacement therapy with desiccated thyroid is completely effective and inexpensive.

The possibility that radiation from therapeutic amounts of radioiodine may subsequently induce cancer of the thyroid has been suggested. The carcinogenic effects of ionizing radiation, particularly with respect to skin and bone, are well known. So far no one has reported cancer of the thyroid subsequent to the use of radioiodine. The isotope has, however, been used only 14 years and has been in general use for only about eight years, so it will require at least 10–20 years' more observation before relevant data will become available. Quimby and Werner (37) investigated patients previously treated with x-ray to the thyroid and queried radiologists who had used this for the treatment of Graves' disease. Although they were able to find several cases of cancer of the skin and a few cases of cancer of the esophagus and trachea which developed after the x-ray treatment of Graves' disease, they were unable to find any cases of cancer of the thyroid. Long-continued exposure to low doses of ionizing radiation appears to be most carcinogenic. The rather brief and intense radiation the thyroid receives from radioiodine is somewhat dif-

ferent and is perhaps less dangerous. A disadvantage upon which adequate data are available is the simultaneous occurrence of Graves' disease and cancer of the thyroid. Pemberton and Black (38), in a large series of cases, found this association to occur in about 0.5 per cent. If one administers radioiodine, one cannot examine the thyroid pathologically, and this small fraction of patients with cancer will be undiagnosed.

With these disadvantages in mind, some fairly general criteria have been proposed for the selection of patients to be treated with radioiodine. The feeling of several groups, with which the author agrees, is that only the following patients should be treated with radioiodine.

1. Patients with recurrent hyperthyroidism. In this group the chance of relapse after another thyroidectomy is quite high, and the technical problems of surgery are such that the occurrence of parathyroid insufficiency or vocal cord paralysis is much greater than with the first operation.

2. Patients with Graves' disease and other complicating disease, e.g., cancer, rheumatic heart disease, etc. In these patients either the life expectancy will be so short that the future development of cancer of the thyroid is extremely remote or else the complicating disease makes surgical thyroidectomy much more hazardous than usual.

3. Patients with Graves' disease in the older age group. In patients under age 45 with Graves' disease, the question of treatment with radioiodine is open to some dispute. Probably in our present state of knowledge it is desirable to treat most of them with propylthiouracil, iodine and subtotal thyroidectomy. There seems little reason, however, to subject a patient 60 years of age to thyroidectomy, and we prefer to treat such patients with radioiodine.

Severe *exophthalmos* in Graves' disease is the most difficult complication to treat successfully. Means (39) stresses the importance of not thyroidectomizing such patients, for in his experience the most severe cases of exophthalmos are seen soon after thyroidectomy. Many physicians will treat such patients with desiccated thyroid, particularly if the basal metabolic rate is only minimally elevated. Such patients frequently tolerate large doses

(250–600 mg. a day) of desiccated thyroid well and appear to improve. Local treatment directed toward the eyes consists in sleeping with the head of the bed elevated and use of dressings over the eyes at night to keep them closed. With these local measures corneal ulcers and even blindness may be prevented. Dehydrating procedures with salt restriction and the use of mercurial diuretics may be employed. Occasionally it is necessary to decompress the orbit. Poppen (40) reported considerable success with his technique. Beierwaltes (41) has reported the results of x-ray therapy to the pituitary, and his data suggest that this is an effective form of treatment. It has been suggested that ACTH is of benefit in the treatment of these patients.

A patient in *thyroid crisis* presents one of the most serious medical emergencies that a physician has to treat. Before the antithyroid drugs were available, this emergency was not an uncommon postoperative problem. We believe that this postoperative problem can now be avoided by insisting that no patient come to thyroidectomy until appropriate treatment with the antithyroid drugs has resulted in euthyroidism and adequate gain in weight.

During the past seven years we have had occasion to treat eight patients who were admitted to the wards in thyroid storm. The following program was carried out in all of them. They were placed in a cool oxygen tent, given morphine in doses of 15 mg. as often as needed to control restlessness and were sponged with ice water and alcohol at least once every hour. Antithyroid therapy was instituted as follows: methylthiouracil was given in doses of 600 mg. at once and then 200 mg. every six hours. Potassium or sodium iodide was administered in doses of 300 mg. one hour after each dose of thiouracil.

Six of these patients were also treated with aqueous adrenal cortical extract in doses comparable to those usually given in the treatment of addisonian crisis. The results in five were dramatic, with a fall in temperature shortly after we first administered the adrenal extract. They all survived.

On the basis of our results in this small series of cases we would suggest that this program of therapy be followed in the management of thyroid storm.

HYPERFUNCTIONING ADENOMATOUS GOITER WITH HYPERTHYROIDISM

In 1913 Plummer (42) published his first report on patients having adenomatous goiters with hyperthyroidism. He advanced the concept that there are two distinct types of hyperthyroidism, one arising from a diffusely hyperplastic thyroid which is characteristic of Graves' disease and the other arising from adenomatous nonhyperplastic goiters. He suggested that the latter should be classified with the cases of toxic goiter heart.

Subsequently, Plummer (43), Boothby (44) and Haines (45) presented analyses of large groups of patients with Graves' disease or exophthalmic goiter and compared them with their analyses of patients with so-called adenomatous goiters with hyperthyroidism. These writers pointed out that both groups of patients have hyperthyroidism. However, they suggested that the hyperthyroidism arising in a patient having a toxic adenomatous goiter is similar to that produced by administering thyroid hormone in excess. The picture in Graves' disease, however, they suggested is something more than a simple excess of thyroid hormone.

Cope, Rawson and McArthur (46) have described studies on a small group of patients having hyperthyroidism which arose from a single hyperfunctioning adenoma.

The etiology of such adenomas is not known. The fact that such adenomatous goiters appear to occur more commonly in the endemic goiter region lends support to the thesis that such adenomas are the end result of prolonged hyperplasia.

The pathology of such thyroids is often quite confusing. We do see hyperthyroidism arising in old nodular goiters which harbor adenomas of various histologic patterns. In most such goiters, one cannot with the routine laboratory techniques define the area in the thyroid responsible for the mischief. On the other hand, the thyroid of a patient with hyperthyroidism arising from a single hyperfunctioning adenoma presents a very characteristic pathologic picture. Grossly we find a single nodule of the thyroid which may vary from 2–6 cm. in diameter. In situ it is usually red and meaty, in contrast to the rest of the thyroid which may be normal

in appearance or even atrophic and relatively pale. On histologic examination such adenomas show the structure of small round follicles with uniformly hypertrophied follicular cells or they may present a frank uniform hyperplasia with loss of colloid and even papillary infolding of the acinar epithelium.

The surrounding normal thyroid tissue appears relatively to absolutely atrophied with normal to smaller than normal acinar cells. Cope and associates (46) observed that when patients with hyperfunctioning adenomas of the thyroid were given tracer doses of radioactive iodine before operation, the radioiodine was concentrated in the adenoma but not in the uninvolved tissue.

There are no other characteristic pathologic changes in patients with this malady.

The patients are usually beyond middle age. Many of them present themselves because of the classic symptoms of hyperthyroidism, i.e., nervousness, weight loss in spite of adequate caloric intake, intolerance to heat and cardiovascular symptoms. Many seek medical help because of cardiovascular symptoms which seem to mask the other symptoms of hyperthyroidism. This situation can probably be attributed to the fact that the hyperthyroidism is insidious in its development and rarely severe.

The physical findings are not as classic as those of Graves' disease. Eye signs are usually absent to minimal. When eye signs do occur they are those which might be attributed to increased levels of thyroid hormone, i.e., dilatation of the pupils, stare and minimal lid lag. These patients do not present true exophthalmos. The skin is usually warm but is not velvety as we find in classic Graves' disease. The thyroid is enlarged. It may be more or less asymmetrically enlarged and harbor multiple nodules. The more classic case in our experience, however, is the patient who presents a discrete nodule in one lobe of the thyroid. In such patients the remaining thyroid tissue is either normal in size or smaller than normal.

The heart in such patients shows the usual signs of hyperthyroidism. Fibrillation and frank cardiac failure are more common in this group than in the younger patients with classic Graves' disease. Since such patients frequently present themselves because of their cardiac symptoms, one should be particularly

interested in the thyroid function of any goitrous patient with symptoms of heart failure. If the heart failure fails to respond to digitalis, careful study of thyroid function is mandatory.

The laboratory findings in this group of patients are similar to those in classic Graves' disease. However, it has been pointed out (47) that the basal metabolic rate may be only slightly elevated and that the PBI level is often just above normal. Unless one is able to compare the uptake of radioactive iodine of one area of the thyroid with that of another, tracer studies with radioactive iodine may not be of much value.

The treatment of this type of hyperthyroidism is ablation of the source of mischief. How to ablate it is not always an easy choice. Since these patients are often in the older age group and have varying degrees of cardiac failure, they are not good risks for surgical treatment. They do not respond to treatment with iodides. Many of them do respond to propylthiouracil. However, Bartels (48) has reported on a significant group of such patients who responded poorly to prolonged treatment with relatively large doses of propylthiouracil and related antithyroid drugs.

Surgical removal often has a dramatic effect in such patients. It should not be done, however, until after the hyperthyroidism is adequately controlled and the cardiac status is judged safe for the strain of anesthesia and surgery.

It has been reported that such patients require significantly larger doses of radioactive iodine for control of their hyperthyroidism than do patients with classic Graves' disease (49). However, in view of the fact that good control of the hyperthyroidism in these patients is obtained slowly with any of the drugs in use, whenever possible we would favor using radioactive iodine in such patients.

THYROTOXICOSIS FACTITIA

Self-induced hyperthyroidism is seen not infrequently in a busy clinic.

Although the cause of the hyperthyroidism is known in that the patients are taking surreptitiously large doses of desiccated thyroid, the cause of such behavior is not known.

One patient whom we have studied, when confronted with the

evidence for this diagnosis, admitted that she had resorted to this sort of trickery to hold the attention of her father who had remarried following her mother's death. Of course that explanation only hints at the patient's basic personality defect.

The patients in whom we have recognized this type of hyperthyroidism have usually described classic symptoms of hyperthyroidism, with nervousness, weight loss and palpitation as their major symptoms.

Physical examination discloses the signs of increased metabolism with a warm moist skin, fine rapid tremor and tachycardia. The patients may present a lid retraction with a stare, dilatation of the pupils and even lid lag. However, they do not have exophthalmos. The one physical finding that should make one suspect self-induced or exogenous hyperthyroidism is the absence of goiter. Indeed, in some of these patients, if they have been taking excessive amounts of thyroid for a long time, the thyroid may be so atrophic that it cannot be felt.

The laboratory studies, if complete, should make the diagnosis. They have elevated metabolic rates, and high serum protein-bound iodine values. When given tracer doses of I^{131}, however, they characteristically concentrate none in the thyroid and excrete all of it in the urine.

The treatment of such patients should be directed at the cause of their abnormal behavior rather than at the hyperthyroidism. Cure may not be achieved without the help of a competent psychiatrist.

STRUMA OVARII

Rarely we may see the hyperthyroid state in a patient with a teratoma in which there is well differentiated thyroid tissue. We have seen only one of these patients, who was later operated on elsewhere.

In such patients the symptoms and findings of hyperthyroidism are characteristic except for the fact that the thyroid is of normal size. Eye symptoms were absent in the one patient we saw. On pelvic examination the teratomatous mass may be easily palpable. However, if the teratomatous lesion occurs elsewhere, it may not be palpable.

The elevated basal metabolic rate and elevated blood iodine associated with minimal uptake of radioiodine in the neck may suggest thyrotoxicosis factitia. However, careful scanning of the body for radioactivity after administering a tracer dose of I^{131} should localize the lesion and indicate the diagnosis of teratomatous thyroid. If the lesion is found in the pelvis, it will naturally fit the criteria of struma ovarii.

After the hyperthyroidism has been controlled with antithyroid drugs, such lesions should be removed surgically.

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